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Long-term Risk of Mortality and Other Adverse Outcomes After Acute Kidney Injury: A Systematic Review and Meta-analysis

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Abstract

Background—Acute kidney injury (AKI) is common in hospitalized patients. The impact of AKI on long-term outcomes is controversial.

Study Design—Systematic review and meta-analysis.

Setting & Participants—Persons with AKI.

Selection Criteria for Studies—MEDLINE and EMBASE databases were searched from 1985 through October 2007. Original studies describing outcomes of AKI for patients who survived hospital discharge were included. Studies were excluded from review when participants were followed for < 6 months.

Predictor—AKI, as defined by acute changes in serum creatinine or acute need for renal replacement therapy.

Outcomes—CKD, cardiovascular disease, mortality.

Results—Forty nine studies that contained a total of 47,017 participants were reviewed. Fifteen of these studies reported long-term data for patients without AKI. The incidence rate of mortality was 8.9 per 100 person-years in survivors of AKI and was 4.3 per 100 patient-years in survivors without AKI (RR 2.59, 95% CI 1.97–3.42). AKI was associated independently with mortality risk in 6 of 6 studies that performed multivariate adjustment (adjusted RR 1.6–3.9) and it was associated with myocardial infarction in 2 of 2 studies (RR 2.05, 95% CI 1.61–2.61). The incidence rate of CKD after an episode of AKI was 7.8 per 100 patient years and the rate of ESRD was 4.9 per 100 patient-years.

Limitations—The relative risk for CKD and ESRD after AKI was unattainable due to lack of follow-up of appropriate non-AKI controls.

Conclusions—The development of AKI, as defined by acute changes in serum creatinine characterizes hospitalized patients at elevated risk of long-term adverse outcomes.

Keywords

Acute renal failure; chronic kidney disease; prognosis

Acute kidney injury (AKI) is a common complication in hospitalized patients. As a conservative estimate, in the U.S. about 17 million admissions a year are complicated by AKI, resulting in additional costs to the health care system of \$10 billion.¹ Furthermore, perhaps partly due to increased recognition, the incidence of AKI has risen from approximately 60 to

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500 per 100,000 population in the last decade.^{2, 3} Concurrently, the incidences of chronic kidney disease (CKD) and end-stage renal disease (ESRD) have increased over the past several years. The association between the development of AKI and higher in-hospital mortality has been well-known for decades and was reported in several studies.⁴⁻¹⁰ However, the association of AKI with long term mortality has received less attention, probably due to the apparent reversibility of the clinical episode as observed by subsequent improvements in serum creatinine.

Studies in experimental animals however demonstrate that AKI causes permanent damage to the microvasculature and subsequent abnormalities in kidney structure and function.¹¹⁻¹³ Through inflammatory and fibrotic signaling pathways, the residual kidney damage can lead to progressive structural kidney damage, which may then predispose to worsening hypertension, proteinuria, and more rapid declines in glomerular filtration rate (GFR),¹⁴⁻¹⁶ all of which are well-known risk factors for cardiovascular disease.¹⁷⁻¹⁹

Currently, little attention is given to AKI after it resolves in clinical practice throughout the healthcare system.²⁰ Understanding the impact of AKI on long term outcomes may identify a segment of patients during hospitalization who are at greater risk of longer term sequelae, guiding follow-up care after discharge. A better understanding of the association may also highlight the importance of preventing AKI. Additionally, if AKI episodes confer increased risk for CKD, cardiovascular disease, and mortality, then therapies known to prevent these outcomes (e.g., angiotensin-converting enzyme [ACE] inhibitors, statins, tighter blood pressure control) could be applied earlier and more aggressively. We conducted this systematic review and meta-analysis to characterize fully the relations between AKI and the long-term outcomes of CKD, cardiovascular disease, and death.

METHODS

This study was performed in accordance with published guidelines for systematic review, analysis, and reporting for meta-analyses of observational studies.²¹

Studies Eligible for Review

A study published from January 1985 onward was eligible for inclusion if it conducted at least 6 months of follow-up of patients after a defined episode of AKI and reported the incidence of at least one of the following outcomes: A) survival; B) cardiovascular events (myocardial infarction, stroke, or congestive heart failure); or C) CKD. We excluded studies that contained fewer than 50 participants in the initial cohort and studies that exclusively focused on “AKI syndromes” (e.g., rapidly progressive glomerulonephritis, hemolytic-uremic syndrome, hepatorenal syndrome, or after bone marrow transplantation). Studies were not required to include a control group without AKI.

Literature Review and Study Selection

We searched the MEDLINE and EMBASE (January 1985 - October 2007) databases using the following terms: Renal Insufficiency, acute; acute kidney, acute kidney failure, acute kidney tubule necrosis, kidney tubule necrosis; survival (explode), prognosis (explode), treatment outcome, recovery of function, follow-up studies. An additional search was performed via the Science Citation Index Expanded on the Web of Science, and the references of all selected articles were reviewed to identify any eligible studies. There was no language or age restriction. Each article chosen by the primary reviewer was reviewed by a second reviewer to confirm eligibility.

Outcome Measures

The primary outcome measures were rates of long-term mortality, cardiovascular events (myocardial infarction [MI], stroke, and congestive heart failure), and incident CKD in survivors of AKI. We assessed rates of each of these endpoints as defined by the number of events in survivors beyond hospitalization or other relevant short-term time period (28 or 30 days) divided by the patient-years of follow-up. Regarding the numerator, many of the studies reported long-term outcomes only in survivors of hospitalization, however, some studies (8 total) only listed cumulative survival for all patients, including those who died in-hospital or within 30 days of admission. In these eight studies,²²⁻²⁹ we subtracted the number of acute deaths from the total number of deaths in the cohort during the entire period of follow-up to obtain the numerator for calculation of the mortality rate. The denominator for the event rate calculation (patient-years) was estimated by addition of the following two values: A) the product of the duration of follow-up and the number of patients who survived until the last follow-up period of the study; B) the product of the duration of follow-up and the number of patients who had died by the time of the last follow-up period divided by 2 (each person who died contributed half of the number of patient-years).

Data collection

Two reviewers (BY, SC) extracted data using a standardized data extraction form. The reviewers extracted data on the characteristics of participants (number, age, sex), clinical setting, type of study (prospective vs. retrospective), dates of enrollment, definition of AKI, definition of CKD, and incidence of the outcomes (mortality, cardiovascular events, and CKD) among participants with and without AKI. Due to significant heterogeneity of definitions of AKI, we created the following 3 categories of AKI severity: Mild AKI, as defined by a threshold change in creatinine $> 0\%$ but $< 50\%$; Moderate AKI, as defined by a change in serum creatinine $\geq 50\%$; and Severe AKI, defined as dialysis-requiring AKI. These groups were not mutually exclusive, as patients who required dialysis in studies that defined AKI as only a change in creatinine above a certain threshold were included with the rest of the patients in the cohort with AKI. Only one study clearly reported long-term survival for those who required dialysis separately from those without while including patients with less severe forms of AKI in the cohort.³⁰ We were not able to separate these participants out in the other cohorts because we did not have individual patient data. Methodological quality was assessed using criteria adapted from Hayden et al.³¹ Any discrepancies on data extraction or quality score were resolved by a third reviewer.

Statistical Analysis

Overall results for each outcome were mathematically pooled, and rate ratios were obtained using techniques that accounted for within and between study heterogeneity (random effects method of DerSimonian and Laird).³² We formally assessed heterogeneity of effects between studies with the Cochran Q and the I^2 statistics.³³ To examine the association between study-level characteristics and outcomes, we fitted random-effects meta-regression models to the natural logarithm of the relative risks by using the meta-regression procedure in Comprehensive Meta Analysis Version 2.0 (Englewood, NJ). At the study level, we evaluated the association of the following patient and study characteristics with mortality outcomes after AKI: clinical setting, definition of AKI, and duration of AKI (transient vs. persistent). In the 3 studies that separated AKI into 2 categories of duration, transient vs. persistent was defined as the following: Welton et al defined transient AKI as return of serum creatinine to within 10% of baseline value at day 3; Liano and Loef et al defined transient AKI as serum creatinine value at the time of discharge returning to preoperative level or below. All meta-analyses were performed using Comprehensive Meta Analysis Software Version 2.0 (Englewood, NJ).

RESULTS

We identified 3,808 citations meeting our search criteria. After excluding 689 duplicate citations, 3119 abstracts were evaluated, and 419 articles were selected for further review (Figure 1). Reasons for exclusion are outlined in Figure 1. Forty eight articles were deemed eligible for this systematic review.^{22-30, 34-73}

Study and patient characteristics from the selected articles are summarized in Table 1. The most common clinical setting for the studies of AKI were critical illness (n=20, 42%), general hospitalized patients (n=10, 21%), and cardiac surgery (n=9, 19%). Most studies were single center (n=41, 85%) and retrospective (n=41, 85%). Five (10%) studies included pediatric patients.

The definitions of AKI varied substantially (Table 2). Maximum length of follow-up ranged from 6 months to 17 years. In-hospital mortality ranged from 6-80%.

Mortality

Fifteen of the 48 studies (31%) provided mortality data on non-AKI controls. The mortality rate in these studies was 8.9 per 100 person-years for patients who survived hospitalization with AKI and 4.3 per 100 person-years for patients who survived hospitalization without AKI (Rate Ratio [RR] 2.59, 95% CI 1.99-3.42) (Figure 2).

Cardiovascular Events and Chronic Kidney Disease

Only two studies examined cardiovascular endpoints after AKI. At 1 year after AKI, 15.4% (56/377) of survivors of AKI and 7.0% (817/11755) of survivors without AKI suffered a MI (relative risk 2.05, 95% CI 1.61-2.61, $I^2 = 0\%$).^{25, 65} One of the two studies examined the risk of MI at 3 points of follow-up (0.5 years, 1 year, 5 years) and the increased risk of MI persisted over time (relative risk 1.6, 1.85, 1.75, respectively, at each time point).

Twenty seven (56%) studies provided data on the incidence of CKD or ESRD in patients who survived hospitalization with AKI. Eleven of these studies reported some form of CKD as an outcome (definitions varied- see footnotes in Table 3), and 23 reported ESRD as an outcome (7 studies reported the incidence of both CKD and ESRD). The rate of CKD after an episode of AKI was 7.8 per 100 patient years and the rate of ESRD was 4.9 per 100 patient-years. In studies that definitively excluded patients with pre-existing CKD, the rate of CKD after AKI was 6.2 per 100 person-years^{28, 37, 44, 58}, and the rate of ESRD was 4.2 per 100 person-years.^{39, 43, 58, 59, 66} None of the studies compared the rate of CKD or ESRD after AKI to patients within the same cohort without AKI, thus we could not determine the rate ratio for CKD or ESRD after an episode of AKI. None of the studies examined the incidence or rate of CKD after AKI that resolved compared to AKI without recovery.

Subgroup and Sensitivity Analyses for Mortality Endpoint

Meta-regression analyses indicated that two study level factors, severity of AKI ($\beta=0.12$, 95% CI 0.004-0.22) and length of follow-up ($\beta= -0.05$, 95% CI -0.09- -0.02), were associated with the magnitude of long-term risk of premature death. In addition to these two study level factors, we also planned *a priori* to examine the relationship between AKI and long-term death among clinical settings and duration of AKI (transient vs. persistent) (Table 3).

Definition of AKI—We examined the association between AKI and death stratified by severity of AKI (Figure 3). The least severe definition of AKI among the studies was a rise in serum creatinine of $\geq 25\%$ or a decrease in creatinine clearance $\geq 10\%$ (3 studies). Mild AKI was associated with approximately a 70% increase in mortality risk, as the rate of death was

6.3 per 100 person-years in survivors of mild AKI and was 3.4 in survivors without AKI (RR 1.67, 95% CI 1.41 - 1.98). The risk of long-term death was nearly three-fold higher in patients with moderate and severe AKI compared to patients without AKI (Figure 3).

Clinical Setting—The long-term mortality rate and rate ratios for death after AKI varied according to the clinical setting, and ranged from 4.5 deaths per 100 person-years in patients who underwent aortic surgery (RR 1.45, 95% CI 1.17-1.79) to 13.1 deaths per 100 person-years in patients who underwent percutaneous coronary intervention (RR 2.89, 95% CI 2.32-3.61) to (Table 3). Compared to those without AKI, the risk for long-term death was significantly greater in patients who survived AKI across every clinical setting. In general, studies were statistically heterogeneous.

Duration of AKI—Three studies examined the relationship between AKI and long-term death stratified by duration of AKI (transient vs. persistent).^{58, 60, 72} Both transient and persistent AKI were associated with an increased risk of death compared to patients without AKI (RR 2.54, 95% CI 2.10-3.06 and RR 2.46, 95% CI 1.68-3.60, respectively) (Table 3). When compared directly, the risk of death was not different in patients with transient or persistent AKI (persistent vs. transient RR 1.15, 95% CI 0.84-1.57).^{58, 60, 72}

Reducing Statistical Heterogeneity—We were able to significantly diminish statistical heterogeneity when we grouped studies by both severity and clinical setting. For example, the I^2 statistic dropped to 0% and 42%, respectively for the following subgroups: A) Moderate AKI in patients undergoing PCI,^{25, 52, 65} B) AKI requiring renal replacement therapy in patients undergoing cardiac surgery.^{53, 57} Although the sample size was lower, the point estimate for the risk of mortality with AKI remained elevated and statistically significant for these sub-groups. The I^2 was 0% in the 3 studies of mild AKI and the 2 studies of AKI after left ventricular assist device placement.

Quality Scores—We assessed the methodological quality of the studies using the criteria by Hayden et al.³¹ Only 33 studies (69%) reported whether patients were lost to follow-up, and 25 of those 33 studies had attrition rates of < 10%. Only 6 studies (13%) adequately adjusted for relevant confounding factors. Three of the 48 (6%) studies met all 6 criteria for quality, 21 (44%) studies met 5 criteria, and 24 (50%) studies met 4 or less of the criteria.

Multivariate Adjustment—Six studies examined the risk of long-term mortality in patients after an episode of AKI, adjusted for factors such as older age, baseline kidney function, history of MI, peripheral vascular disease, diabetes, and hypertension, among others. The risk for long-term death in patients with AKI was consistently greater than patients without AKI, with all adjusted point estimates exceeding 1.6 after multivariate adjustment.^{25, 26, 51, 52, 60, 72} Three studies^{25, 51, 52} used logistic regression models and reported adjusted odds ratios and 3 studies^{26, 60, 72} used Cox Proportional Hazards models and reported adjusted hazards ratios. In these six studies, the independent strength of association between AKI and long-term death was similar to the strength of association between other established risk factors and long-term death.

DISCUSSION

This study demonstrates that patients who survive AKI have a higher rate of long-term mortality, and other adverse outcomes than patients who survive hospitalization without AKI. The associations were consistent in every clinical setting. With increasing severity of AKI, the association between AKI and death was even stronger, and the association with long-term mortality seemed to be present even in patients with more rapidly reversible AKI. These findings expand upon the results from our previous systematic review that demonstrated the

increased risk of short-term death associated with very small changes in serum creatinine.⁷⁴ Thus, all severities of AKI, even the most mild forms, are associated with both short and long-term survival.

Although we demonstrated a consistent, reproducible association between AKI and long-term adverse outcomes, this does not imply causality. Patients with AKI are often sicker than those without AKI, and AKI is often the complication of multiple organ dysfunction. However, in studies that performed multivariate analyses, the strength of association between AKI and mortality was similar, or greater than that associated with other established risk factors including diabetes, peripheral vascular disease, and chronic obstructive lung disease. Thus, at the very least, AKI can serve as an easily assessable prognostic marker of increased long-term mortality risk.

It remains possible that some of the association between AKI and poor long-term outcomes is causal in nature. As already mentioned, the relationship remained present after controlling for important co-morbidities. In addition, there is biologic support for this relationship as data from experimental animals does demonstrate that AKI can induce tissue injury in other organ systems such as the heart (apoptosis),⁷⁵ lungs (loss of pulmonary vascular integrity),⁷⁶ and kidney (fibrosis).^{11, 12} Despite the reversible nature of clinical AKI where serum creatinine returns to baseline after the episode, AKI may result in permanent injury to other vital organs and thus affect future survival.

If AKI is causally associated with long-term mortality, and not simply a marker for unmeasured risk factors, the most common pathway would be through progression to CKD after an episode of AKI. Although 27 studies examined the cumulative incidence of CKD or ESRD in survivors of AKI, we could not calculate risk ratios for the development of CKD because none of the studies included comparable controls without AKI.

The results of any systematic review are limited by the quality of the primary studies. We assessed the methodologic quality of these studies using accepted criteria. In 41 of the 48 studies, data were collected retrospectively using existing health records. The majority of the studies were single-center studies, thus limiting total achievable sample size and generalizability. Fifteen of the 48 studies did not report whether patients were lost to follow-up, and only 6 of the 15 studies (40%) that followed non-AKI patients adequately adjusted for relevant confounding factors. Nonetheless, the lower bound confidence interval of the risk ratio remained above 1 for all studies that presented adjusted long-term mortality, supporting a consistent relationship. Primary articles used several different definitions for both AKI and CKD, complicating the clinical application of these results. However, the effect was observed across all thresholds of AKI definition, and all-cause mortality is an outcome less prone to bias. It is unfortunate that no studies were able to provide a point estimate for the hazard ratio of CKD or ESRD because of a lack of non-AKI controls. Few studies excluded patients with prior CKD from the reported cumulative incidence of CKD. Also, no studies examined the pattern or slope of GFR decline after AKI over time. This type of analysis would help enlighten the medical community as to whether AKI evolves into CKD abruptly and then plateaus, whether GFR declines in a “step-function”, or whether GFR decreases at a constant rate after an episode of AKI. Many studies also did not have access to a previous “baseline” measure of renal function, prior to the acute illness that would have increased the sensitivity of AKI diagnosis. Most patients were classified as AKI if kidney function deteriorated further after the start of hospitalization, thus representing a more severe phenotype of AKI. Finally, our point estimates should be interpreted with caution, as most pooled estimates invoked a great deal of statistical heterogeneity. We attributed the cause of heterogeneity to the interaction between the definitions of AKI (severity) and clinical setting, as we were able to substantially ameliorate statistical heterogeneity when we accounted for these factors.

While the precise risk for adverse outcomes and death may not be known exactly from our meta-analysis, the consistency of our results suggest that patients who suffer AKI should be monitored closely even after recovery of kidney function for the development of CKD, myocardial infarction, and other potential mediators of poor long-term survival. Future longitudinal studies of AKI should examine larger cohorts of patients (via multi-center prospective studies), with appropriate non-AKI controls, repeated follow-up, and utilize both continuous outcomes (measures of kidney function) and hard-outcomes such as CKD, ESRD, cardiovascular events, and death to truly elucidate the consequences of AKI. Future studies should also rigorously adjust for the level of baseline kidney function when determining the impact of AKI towards CKD. If the suggestion of harm from AKI from this meta-analysis is validated, then determining effective treatment strategies to prevent AKI and adverse outcomes following AKI will be the next challenge that lies ahead for nephrologists and intensivists.

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Figure 1. Flow diagram of studies with long term outcomes of AKI that were considered for inclusion

Figure 2. Pooled rate ratio of long-term mortality for survivors of AKI

Overall RR 2.62 (95% CI 1.99-3.45); $I^2 = 86\%$

Abbreviations: Txp, transplantation; RRT, renal replacement therapy;

PCI, Percutaneous intervention; LVAD, left ventricular assist device AKI, acute kidney injury.

Figure 3. Pooled rate ratios for long-term death by severity of AKI

A. Mild AKI (Rise in creatinine by 25% or drop in creatinine clearance of > 10%)

RR 1.67 (95% CI 1.41-1.98); $I^2 = 0\%$

B. Moderate AKI (Rise in creatinine by > 50%, > 100%, > 1.0 mg/dl, or creatinine concentration of > 1.7 mg/dL)

RR 2.70 (95% CI 1.77-4.12), $I^2 = 89\%$

C. Severe AKI (RRT-requiring)

RR 3.09 (95% CI 2.20-4.33), $I^2 = 66\%$

Table 1
Characteristics of Long-term Prognosis Studies of Acute Kidney Injury (AKI)

Source	Clinical Setting	# of Patients	Years of enrollment	Multicenter	Prospective Study	Study population	Age [*] (range)	Controls [†]	Men (%)
Abosaif et al ³⁴	Critically ill	183	2002-2003	No	No	Adults	65	Yes	68
Ahlstrom et al ³⁵	Critically ill	703	1998-2002	No	No	Adults	(43-73)	No	..
Akposso et al ³⁶	Critically ill	381	1971-1996	No	No	Adults	85	No	50
Alric et al ³⁷	Post Aortic stents	315	1994-2001	No	No	Adults	72	No	92
Askenazi et al ³⁸	Hospitalized	245	1998-2001	No	No	Children	6.4	No	..
Bagshaw et al ³⁹	Critically ill	5693	1999-2002	Yes	No	Adults	65	Yes	63
Bagshaw et al ⁴⁰	Critically ill	240	1999-2002	Yes	No	Adults	66	No	58
Bahar et al ⁴¹	Cardiac surgery	168	1991-2001	No	No	Both	56	No	74
Barratt et al ⁴²	Cardiac surgery	65	1984-1996	No	No	Adults	69	No	92
Benoit et al ⁴³	Critically ill	270	1997-2002	No	No	Adults	63	No	62
Bhandari et al ⁴⁴	Hospitalized	1095	1984-1995	No	No	Adults	63	No	61
Brivet et al ⁴⁵	Critically ill	360	1991	Yes	Yes	Adults	60	No	67
Chertow et al ⁴⁶	Critically ill	132	1991-1993	No	No	Adults	60(17)	No	42
Cosentino et al ⁴⁷	Critically ill	363	1988-1991	No	Yes	Adults	60	No	52
Dahlberg et al ⁴⁸	Hospitalized	90	NA	No	No	Adults	(21-88)	No	70
El-Shahawy et al ⁴⁹	Critically ill	222	1991-1997	Yes	No	Adults	55	No	69
Frost et al ⁵⁰	Hospitalized	419	1977-1988	No	No	Both	52	No	64
Gonwa et al ⁵¹	Liver transplant	1535	1985-1999	No	No	Adults	48	Yes	..
Gopal et al ⁵²	Critically ill	250	NA	Yes	No	Both	59	No	65
Gruberg et al ⁵³	PCI	439	NA	No	Yes	Adults	70	Yes	68
Gupta et al ⁵⁴	PCI	9067	1997-2001	No	No	Adults	72	Yes	50
Hamel et al ⁵⁵	Critically ill	490	1989-1994	No	No	Adults	61	No	42
Hein et al ⁵⁶	Cardiac surgery	2683	2001-2003	No	No	Adults	67	Yes	68
Jones et al ⁵⁷	Critically ill	408	1991-1995	No	No	Adults	54	No	60
Kaltenmaier et al ⁵⁸	Cardiac surgery	227	1988-1995	No	No	Adults	44	Yes	78
Khan et al ⁵⁹	Hospitalized	311	1989-1990	No	No	Adults	(28-80)	No	55
Korkela et al ⁶⁰	Critically ill	62	1992-1993	No	No	Adults	56	No	69

Source	Clinical Setting	# of Patients	Years of enrollment	Multicenter	Prospective Study	Study population	Age [*] (range)	Controls [†]	Men (%)
Landoni et al ⁵⁷	Cardiac surgery	7846	1998-2003	No	No	Adults	67	Yes	55
Liano et al ⁵⁸	Hospitalized	413	1977-1992	No	No	Adults	58	No	66
Lindsay et al ²⁵	PCI	5967	1994-2000	No	No	Adults	64	Yes	67
Lins et al ⁵⁹	Hospitalized	293	NA	Yes	Yes	Adults	68	No	63
Loef et al ⁶⁰	Cardiac surgery	145	1991	No	No	Adults	62	Yes	75
Luckraz et al ⁶¹	Cardiac surgery	92	1997-2003	No	No	Adults	68	No	67
McCarthy et al ⁶²	Critically ill	142	1977-1979	No	No	Adults	59	No	73
Miller et al ⁷⁷	Hospitalized	118	1980-1990	No	No	Children	(3 d-5 y)	No	59
Morgera et al ⁶⁴	Critically ill	979	1993-1998	No	No	Adults	60	No	65
Noble et al ⁶⁹	Critically ill	117	1984-1991	No	Yes	Adults	52	No	71
Paramesh et al ²⁹	Liver transplant	186	1988-2000	No	No	Adults	53	No	63
Rihal et al ⁶⁵	PCI	7586	1996-2000	No	No	Adults	68	Yes	69
Rocha et al ²⁶	Lung transplant	169	1992-2000	No	No	Adults	44	Yes	47
Schiffi et al ⁶⁶	Critically ill	425	1990-2001	No	Yes	Adults	65	No	66
Soares et al ⁶⁷	Critically ill	309	2000-2004	No	Yes	Adults	61	No	61
Sraer et al ⁶⁸	Critically ill	381	1971-1996	No	No	Adults	80	No	50
Tariq et al ⁷⁰	Community/Hospitalized	562	2003	Yes	No	Adults	76	No	54
Topkara et al ²⁷	Cardiac surgery	65	1996-2004	No	No	Adults	54	Yes	77
Turney et al ²⁸	Hospitalized	1347	1956-1988	No	No	Adults	41	No	57
Welten et al ⁷²	Cardiac surgery	952	1995-2006	No	No	Adults	66	Yes	80
Wong et al ⁷³	Liver transplant	102	1999-2004	No	No	Adults	49	Yes	64

Abbreviations: **BMT**, Bone marrow transplant, **PCI**, Percutaneous intervention, **SC**, single center, **MC**, Multi-center, **NA**, ***.

* Mean or median age as reported by the authors.

† Controls are patients from the same clinical setting without AKI as defined by the authors.

Table 2

Long-term Outcome Studies of Acute Kidney Injury

Source	CKD Patients Excluded from Study (threshold reported if yes)	AKI Definition *	Follow up, y		Max.	Mortality %		Renal Outcomes		Lost to f/u %
			Mean/Median			In-Hospital or 30-d	Hospital Survivors (time point reported)	CKD%	ESRD%	
Abosati et al ³⁴	No	RIFLE	...		0.5	52	13 (0.5 yrs)	...	...	0
Ahlstrom et al ³⁵	No	RRT	4		6.4	41 ^a	70 (5 yrs)	...	...	41
Akposso et al ³⁶	No	S Cr >1.35b	...		12	40	77 (6 yrs)	...	...	53
Alric et al ³⁷	No	Δ S Cr > 20%	2.4(2)		5	24 ^a	...	16 ^c	...	64
Askenazi et al ³⁸	Yes (not defined)	Δ S Cr > 0.3	...		5	29	20 (3-5 yrs)	12 ^d	9	0/77 ^e
Bagshaw et al ³⁰	No	S Cr > 1.7	...		1	24	5.5 (1 yr)	...	...	0
Bagshaw et al ³⁹	No	RRT	...		1	59	27.5 (1 yr)	...	9, 14 ^f	0
Bahar et al ⁴⁰	No	RRT	6(3)		13	80	41 (10 yrs)	15 ^g	24	0
Barratt et al ⁴¹	No	RRT or S Cr >6.8	...		5	75	56 (5 yrs)	69 ^h	6	0
Benoit et al ⁴²	No	RRT	...		0.5	62	24 (0.5 yrs)	...	...	25
Bhandari et al ⁴³	Yes (not defined)	RRT or S Cr >6.8	...		5	41	59 (5 yrs)	...	17	...
Brivet et al ⁴⁴	Creat > 3.4 mg/dl	S Cr > 3.5 or 100%	...		0.5	58 ⁱ	13 (0.5 yrs)	28 ^j	...	43
Chertow et al ⁴⁵	No	RRT	...		1	70	19 (1 yr)	...	33	2
Cosentino et al ⁴⁶	No	RRT	...		1	...	...	...	35	...
Dahlberg et al ⁴⁷	No	RRT	...		13	55	29 (3 yrs)	...	25	...
El-Shahawy et al ²²	Creat > 2.0 mg/dl	Δ S Cr >1	...		1	...	46.5 (1 yr)	...	...	...
Frost et al ⁴⁸	No	RRT	...		5	46 ^a	37 (5 yrs)	...	...	...
Gonwa et al ⁴⁹	No	RRT	...		1	6 ^a	7.4 (1 yr)	...	16	...
Gopal et al ⁵⁰	No	S Cr >3.4	2.8		5	66	33 (2.8 yrs)	...	...	39
Gruberg et al ⁵¹	No (all pts in study with CKD; creat ≥ 1.8 mg/dl)	Δ S Cr > 25%	...		1	9	19.2 (1 yr)	...	18 ^k	0
Gupta et al ⁵²	No	Δ S Cr > 1	3		...	NA	19 (3.2 yrs)	...	...	...
Hamel et al ²³	No	RRT	...		0.5	...	73 (6 yrs)	...	...	0
Hein et al ⁵³	No	RRT	3		...	6.3	14 (3 yrs)	...	...	5
Jones et al ⁵⁴	No	RRT	...		0.5	62	4.5 (0.5 yrs)	...	9	1

Coca et al.

Source	CKD Patients Excluded from Study (threshold reported if yes)	AKI Definition *	Follow up, y		Mortality %		Renal Outcomes		Lost to f/u %
			Mean/Median	Max.	In-Hospital or 30-d	Hospital Survivors (time point reported)	CKD%	ESRD%	
Kaltenmaier et al ⁵⁵	No	RRT	...	0.5	44 ^d	42 (0.5 yrs)	...	...	...
Khan et al ²⁴	Creat > 2.25 mg/dl	S Cr ≥ 3.4	...	2	...	69 (2 yrs)	...	...	0
Korkeila et al ⁵⁶	No	RRT	...	5	45	35 (5 yrs)	...	15	0
Landoni et al ⁵⁷	No	RRT	3.5	...	67	14 (3.5 yrs)	...	9	5
Liano et al ⁵⁸	Creat > 1.4 mg/dl	S Cr > 2	7	22	55	50 (10 yrs)	19m	2	5 ⁿ
Lindsay et al ²⁵	Creat > 1.2	S Cr > 50%	...	1	...	9.5 (1 yr)	...	...	15
Lins et al ⁵⁹	Creat > 2.0 mg/dl	S Cr > 2	...	1	51	22 (1 yr)	...	12	...
Loef et al ⁶⁰	No	↑ S Cr ≥ 25%	...	8.3	15	16 (8.3 yrs)	...	...	10
Luckraz et al ⁶¹	No	RRT	...	5	42	9.5 (5 yrs)	...	5	1
McCarthy et al ⁶²	No	RRT	...	1	68 ^p , 48 ^q	35 ^p , 43 ^q (1 yr)	...	22 ^p , 4 ^q	0
Mileret al ⁷⁷	No	...	...	12.5	24	6(...)	47 ^r	...	29
Morgera et al ⁶⁴	No	RRT	2.5	...	69	42 (5 yrs)	31 ^s	10	10 ^t , 47 ^u
Noble et al ⁶⁹	No	RRT	5	17	79	33 (N/A)	...	9	7
Paramesh et al ²⁹	Yes (not defined)	RRT	6	...	...	40 (1 year)	46 ^v	23	0
Rihal et al ⁶⁵	No	↑ S Cr ≥ 0.5	...	5	23.5	15.2 (5 years)	...	...	6.5
Rocha et al ²⁶	Yes (GFR < 90)	↑ S Cr 100%	3(2.5)	10	...	49.5 (5 years)	...	...	0
Schiff et al ⁶⁶	Creat > 1.3 mg/dl	RRT	1	1	47	34 (1 year)	...	1	2
Soares et al ⁶⁷	No	Bellomo criteria	...	0.5	64	24 (0.5 yrs)	26 ^v	8.5	...
Sraer et al ⁶⁸	No	↑ S Cr 100%	1.5	8	40	63 (5 years)	...	5	...
Tariq et al ⁷⁰	No	S Cr > 50%	0.5	0.5	34	27 (0.5 yrs)	...	...	...
Topkara et al ²⁷	No	RRT	...	7	...	42.2 (7 years)	...	...	...
Turney et al ²⁸	Yes (not defined)	RRT/ S cr > 6.8	...	1	...	49.5 (1 year)	8 ^s	...	...
Welten et al ⁷²	Yes (CrCl < 30)	↓ GFR > 10%	6(3)	10	8	38 (10 years)	...	...	...
Wong et al ⁷³	No	RRT	...	1	69	12 (1 yr)	...	...	7

Abbreviations: y, years; ..., not available, RRT, renal replacement therapy, f/u, follow-up, GFR, glomerular filtration rate, S Cr, serum creatinine (in mg/dL), CKD, chronic kidney disease, ESRD, end-stage renal disease;

Conversion factors for units: serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$, glomerular filtration rate in $\text{mL}/\text{min}/1.73\text{m}^2$ to $\text{mL}/\text{s}/1.73\text{m}^2$, $\times 0.01667$.

Footnotes: Bellomo criteria- Serum creatinine > 1.44 mg/dl and urea > 48 mg/dL and/or UO < 800 mL/d or UO < 200 mL/6 hours. If had CKD baseline then AKI definition is increase in serum creatinine > 0.72 mg/dL or urea > 24 mg/dL and /or UO < 800 mL/d or UO < 200 mL/6 hours.

* all serum creatinine values are in mg/dl

a % of deaths in 30 to 100 days

b In Patients with normal baseline renal function ($\Delta \text{SCr} > 50\%$ or $0.72\text{mg}/\text{dl}$ in patients with baseline CKD)

c creat >130 mmol/l in patients with normal baseline kidney function

d creatinine clearance < 90 $\text{mL}/\text{min}/1.73 \text{ m}^2$

e 0% loss to follow-up for ESRD or death endpoints, 77% loss to follow-up for CKD endpoint

f 9% ESRD in patients with normal baseline kidney function, 14% in those with baseline CKD

g “kidney function did not recover to normal”

h renal impairment necessitated continued review in a nephrology outpatient clinic”

i Only in patients who had dialysis-requiring AKI

j Serum creatinine > 1.7 mg/dL

k Only in patients who had dialysis-requiring AKI

m Serum creatinine > 1.4 mg/dl

n creat > 110 mmol/l

p cohort between 1977-1979

q cohort between 1991-1992

r “impaired renal function”

s not defined

t entire cohort

u loss to F/U for assessment of kidney function

v eGFR < 60 $\text{mL}/\text{min}/\text{m}^2$ for at least 3 months

Table 3

Mortality Rates and Rate Ratios

Subgroup	Number of Studies	Deaths/Person-years (Deaths per 100 person-years)		# of Studies Demonstrating Harm		Rate Ratio	Heterogeneity (I ²)
		AKI	No-AKI	Point Estimate > 1	Lower Bound 95% CI > 1		
Overall	15	685/7665 (8.9)	3739/87014 (4.3)	15	12	2.59 (1.97-3.42)	86%
Definition of AKI							
At least Mild	3	250/3972 (6.3)	340/9908 (3.4)	3	3	1.67 (1.41-1.98)	0%
At least Moderate	6	325/2928 (11.1)	2980/67488 (4.4)	6	4	2.73 (1.81-4.14)	90%
Severe (RRT)	7	148/1079 (13.7)	590/13351 (4.4)	7	6	3.04 (2.13-4.33)	60%
Clinical Setting							
Critical Illness	2	48/347 (13.8)	173/3743 (4.6)	2	1	2.41 (1.50-3.85)	0%
Cardiac Surgery	3	97/1335 (7.3)	327/11956 (2.7)	3	3	3.72 (1.49-6.94)	85%
PCI	4	218/1670 (13.1)	2793/66350 (4.2)	4	4	2.89 (2.32-3.61)	49%
Non-renal transplant	3	92/1632 (5.6)	204/2884 (7.1)	3	1	1.89 (0.9-3.96)	82%
LVAD	2	59/581 (10.2)	79/1582 (5.0)	2	2	2.15 (1.53-3.03)	0%
Aortic Surgery	1	171/3840 (4.5)	163/5290 (3.1)	1	1	1.45 (1.17-1.79)	N/A
Duration							
Transient vs. none	2	201/2298 (8.7)	301/9645(3.1)	2	2	2.54 (2.10-3.06)	0%
Persistent vs. none	2	124/1370 (9.1)	301/9645 (3.1)	2	2	2.46 (1.68-3.60)	49%
Persistent vs. transient	3	186/2150 (8.7)	232/2923 (7.9)	2	1	1.15 (0.84-1.57)	45%

Mild AKI: Rise in creatinine by > 25% or drop in creatinine clearance of > 10%

Moderate AKI: Rise in creatinine by > 50%, > 1.0 mg/dL, or creatinine concentration > 1.7 mg/dL

Severe AKI: Need for RRT

Transient AKI: Welton et al defined as recovery within 10% of baseline value at day 3; Liano and Loef et al defined serum creatinine value at the time of discharge returned to preoperative level or below.

Persistent AKI:

Abbreviations: AKI, acute kidney injury; PCI- percutaneous coronary interventions; LVAD- left ventricular assist device; RRT- AKI requiring dialysis